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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/722,820	11/25/2003	Bruce N. Ames	18941H-003830US	9373

20350 7590 11/29/2007

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EXAMINER	
BETTON, TIMOTHY E	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
11/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/722,820	**Applicant(s)** AMES ET AL.	
	Examiner Timothy E. Betton	**Art Unit** 1614	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 05 September 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: 1-58.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

Continuation of 11. does NOT place the application in condition for allowance because:
Applicants' remarks filed 5 September 2007 have been duly acknowledged and made of record.
Specifically, applicants respectfully request reconsideration of remarks presented in the section "Primary N-hydroxylamines exhibit superior properties", beginning on page 15 of Applicants' response dated 16 October 2006. However, the rejection put forth in the previous action by Examiner is sufficiently maintained in light of applicants' current response. Applicants' response is absent of any explanation, which adequately challenges the 103(a) rejection as set forth in the office action of 5 June 2007.
Instant claims 1-58 are made obvious by the extensive and explanatory embodiments drawn to N-hydroxylamines of the Krishna et al.and Schmidl et al. references (already made of reference). The teachings, representative modifications, and motivation of Krishna et al. and Schmidl et al. are prima facie obvious over the central issue and objective of the claimed invention. This alleged special property of N-hydroxylamines attributed to senescence is synonymous to the same well-known characteristic of N-hydroxylamine moiety that protects mammalian cells exposed to reactive oxygen species, such as super oxide, hydrogen peroxide, and organic hydroperoxides, etc. Applicants' argue that there is no "first " advantage (over the prior art) in pharmaceutical compositions comprising primary N-hydroxyl amines from which a second advantage (in this case, the ability to delay senescence) would naturally flow. However, the instant claims are absent of any indication drawn to an alleged "first ' advantage from which a "second " advantage would naturally flow (Remarks pg 16). Prior to the instant limitations of claims 56 and 57, there is no indication in the instant claims or in the objective of claimed invention, which is drawn to any "first" advantage.
Accordingly, for the reasons already made of record, the rejections as set forth in the earlier action of 5 June 2007 are maintained.

Claim Rejections -35 USC§ 103(a)
The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:
(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krishna et al. in view of Schmidl et al. of U.S. Patent No. 5,504,072.
Krishna et al. teach of the protective effects of inter alia hydroxylamines. Krishna et al. teach that cellular damage may result from the cytotoxicity of reactive oxygen species, (see column 1, page 3477). Krishna et al. also teach that the reactive oxygen species are byproducts of normal processes in aerobic environments, and when there are imbalances in these reactive oxygen species oxidative stress results to cells, (see page 3477). Krishna et al. also disclose that hydroxylamines have been shown to protect mammalian cells exposed to reactive oxygen species, such as super oxide, hydrogen peroxide, organic hydroperoxides, and redox cycling and anticancer agents, (see column 2, page 3478). In addition, Krishna et al. teach of screening methods to test the effectiveness of hydroxylamines to provide protection to mammalian cells that are exposed to a reactive oxygen species, namely hydrogen peroxide. The results were performed with an in vitro assay, (see column 2, page 3478). In the assay model of this teaching the efficacy of the antioxidant, such as hydroxylamine, was evaluated by exposing the cells to a reactive oxygen species, namely hydrogen peroxide, and assessing the viability of the cells both in the absence and in the presence of a fixed concentration of the test compound, (see column 2, page 3480). The assessment would compare the amounts of the reactive oxygen species present, while the instant invention is comparing the amounts of the antioxidant of the hydroxylamine present after contact with the cells. There are many ways to measure the concentration of an assay, such as a decrease in the concentration of the unwanted species or compound, (as in Krishna et al.) or still by measuring the concentration of the antioxidant compound of the hydroxylamine (as is obviously claimed by applicant).
The instant claims differ only in screening methods for primary hydroxylamines whereas the prior art reference of Krishna et al. are directed to screening methods with the utilization of secondary amines. The skilled artisan would most certainly have been motivated from the screening methods of Krishna et al. to employ other antioxidant or cytoprotective hydroxylamine compounds to protect cells from the deleterious effects due to oxidative damage due to inter alia, reactive oxygen species. The generation of reactive oxygen species, as taught by Krishna et al., is evident in many various biochemical and aerobic environments. Accordingly, if a cellular event such as from a variety of scenarios, for instance ischemia or inflammation or cancer or cytokines or still other events, which can generate and cause oxidative damage to a cell, would be obviously protected with the presence of hydroxylamine compounds, as clearly taught by Krishna et al. Clearly, it would have been obvious to the skilled artisan to utilize other hydroxylamine compounds and derivatives, which would obviously include primary hydroxylamine compounds and their derivatives, because the reaction between the oxidative damage lies between the reactive oxygen species and they hydroxylamine moiety. The skilled artisan would additionally be motivated to use primary hydroxylamine compounds and their derivatives especially since the hydroxylamine moiety of a primary hydroxyl amine is less sterically hindered than a primary hydroxylamine compound. In addition, one having ordinary skill in the art would have been motivated to use primary N-hydroxylamines to offset the deleterious effects of reactive oxygen species to cells when the prior art specifically teaches that secondary N-hydroxylamines also perform this very same function. For this reason, the skilled artisan would expect that compounds with primary N-hydroxylamines would also reduce the effects of reactive oxygen species to cells because the only structural difference lies with the presence of absence of a hydrogen atom attached to the functional group of the N-hydroxylamine moiety. Moreover, the skilled artisan would even expect that the structurally related compounds of primary N-hydroxylamines would react more readily than the secondary N-hydroxylamines due to the absence of a secondary carbon-containing moiety, thus decreasing the steric hindrance of the secondary N-hydroxylamine. The amount and level of skill involved with substituting "bulky" groups, such as alkyl moieties for less "bulky" groups, such as a hydrogen atom, is well within the level of the skilled artisan. In fact, the replacement of an alkyl group for a hydrogen atom is expected and obvious, rather than as purported by applicants as unexpected and nonobvious because of the difference in steric hindrance between a primary N-hydroxylamine and a secondary N-hydroxylamine. Furthermore, one having ordinary skill in the art would have been motivated to use closely related N-hydroxylamine-containing compounds and their derivatives, which clearly embraces primary N-hydroxyl amines due to the fact that the reaction between

the unwanted reactive oxygen species, is with the N-hydroxylamine-containing moiety.

Schmidl et al. teach of the pharmaceutical administration of vitamins, minerals, carbohydrates, proteins, and amino acids, and namely carnitine. Schmidl et al. teach that carnitine is to be included in nutritional compositions because it possesses advantageous properties to an individual, namely improved energy metabolism, (see column 7, lines 1-21 and Table 8). "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose,
in order to form a third composition to be used for the very same purpose ....
[T] he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). Since carnitine and nitroxide compounds are shown to have advantageous properties to an individual, the skilled artisan would be motivated to combine them together for administration.
Conclusion
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy E. Betton whose telephone number is (571) 272-9922. The examiner can normally be reached on Monday-Friday 8:30a - 5:00p.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571) 272-0718. The fax phone
number for the organization where this application or proceeding is assigned is 571-273-8300.
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a
USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

TEB

Ardin H. Marschel 11/26/07
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER